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Application No. 10/777,792
Amendment dated February 6, 2007
Reply to Office Action of August 7, 2006

REMARKS

Claim 131 has been amended for improved clarity as discussed in more detail below. Claims 119-143 remain pending. Applicant responds to the Examiner's comments in the order made. Lack of comment on any subject raised by the Examiner should not be construed as acquiescence in the Examiner's position.

¶1. Priority

For purposes of responding to the present office action, applicant accepts the Examiner's determination of priority. Applicant reserves the right to show an earlier date of invention should this become relevant in subsequent proceedings.

¶2. 35 U.S.C. § 112, second paragraph

Claim 131 has been amended to clarify that the conjugate and adjuvant referred to in this claim are separate entities.

3. 35 U.S.C. § 103

Claims 119, 121-124, 126-131, 134-137 and 139-143 stand rejected as obvious over Chain as evidenced by Alberts in view of Frenkel, Collier and Van den Dobbelsteen. Chain is alleged to teach immunizing with a chimeric peptide including a T-helper epitope and a peptide from the N or C terminus of Aβ. Chain is also alleged to teach adjuvants and dosages in a range of 0.5 microgram to 1 mg/kg. The Examiner acknowledges Chain does not teach Aβ1-7 or CRM197. Frenkel is alleged to teach that residues Aβ1-7 encompass an important site of Aβ for the generation of antibodies capable of inhibiting Aβ aggregation. Collier and Van den Dobbelsteen are cited as teaching use of diphtheria toxin in vaccines including CRM 197. The Examiner alleges that it would have been obvious to modify the chimeric Aβ peptides taught by Chain by conjugating the Aβ1-7 peptide taught by Frenkel to CRM197 as taught by Collier and Van den Dobbelsteen to enhance the immune response to Aβ peptide in view of Frenkel's

alleged teaching that Aβ1-7 comprises a region particularly important for inhibiting the fibrillogenic and neurotoxic properties of the Aβ peptide. The Examiner further alleges that one would have been motivated to produce Aβ1-7 conjugates not only to produce production of anti-amyloidogenic properties, but also for the benefit of treating Alzheimer's disease in view of Chain's citation to a paper by Schenk (the present inventor) at p. 6 of the office action. The Examiner alleges that one would have had a reasonable expectation of success from the numerous teachings of the references that toxin conjugated peptides have an enhanced immune response. This rejection is respectfully traversed.

Chain discusses a strategy of administering short peptides of Aβ from the N or C-terminus to elicit an immune response against Aβ without eliciting an immune response against APP (see p. 11, first sentence). The desired peptides should preferably include only two or three amino acids, and perhaps up to five to minimize the amount of antibody produced which reacts with precursor APP protein (p. 12, second paragraph).

Frenkel reports that two antibodies with epitopes of residues 3-6 of Aβ were able to inhibit aggregation of Aβ but a third antibody (2H3) with the epitope across residues 1-7 of Aβ did not inhibit aggregation.

It is respectfully submitted that one would not have been motivated to replace Chain's short peptide of up to five residues of Aβ with Aβ1-7 because Chain warns of the undesired outcome that using a longer peptide may generate antibodies that bind APP as well as Aβ causing undesired side effects, thus teaching away from the claimed invention. A reference teaching away from an invention is strong evidence of non-obviousness, in fact, the very antithesis of obviousness, to which a rebuttal should not even be required. *In re Buehler*, 185 USPQ 781 (CCPA 1975); *In re Hedges*, USPQ 685, 687 (Fed. Cir. 1986).

Moreover, Frenkel confirms Chain's concerns by reporting the presence of an epitope between residues of 3-6 of Aβ. An immune response against this epitope, which is not end specific, would also be an immune response against APP. The existence of such an epitope reinforces Chain's warning that no more than five amino acids should be included to prevent inducing an immune response against APP. Thus, using a longer peptide than taught by Chain would defeat Chain's goal of producing only antibodies specific to the N-terminus of Aβ.

Where, as here, the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. *In re Ratti,* 123 USPQ 349 (CCPA 1959).

It is respectfully submitted that one would not have been motivated to replace Chain's short peptide of up to five residues of Aβ with Aβ1-7 because Chain warns of the undesired outcome that using a longer peptide may generate antibodies that bind APP as well as Aβ causing undesired side effects. Moreover, Frenkel confirms Chain's concerns by reporting the presence of an epitope between residues of 3-6 of Aβ. An immune response against this epitope, which is not end specific, would also be an immune response against APP. The existence of such an epitope reinforces Chain's warning that no more than five amino acids should be included to prevent inducing an immune response against APP. Thus, using a longer peptide than taught by Chain would defeat Chain's goal of producing only antibodies specific to the N-terminus of Aβ. Where, as here, the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. *In re Ratti,* 123 USPQ 349 (CCPA 1959).

Moreover, Frenkel does not attach any particular significance to using an Aβ 1-7 fragment to generate antibodies with anti-aggregating properties. The two antibodies reported to have anti-aggregating activity had an epitope specificity of residues 3-6 of Aβ not 1-7. The antibody binding to an epitope across residues 1-7 of Aβ (2H3) did not have aggregating activity. Thus, Frenkel does not suggest any particular advantage of using a 1-7 Aβ peptide to generate antibodies with aggregating properties in any event.

The motivation for combining the references appears to rely on the benefit of using the claimed compositions for treatment of Alzheimer's disease. However, it is respectfully submitted that the references do not provide a reasonable expectation of success that this could be achieved. Chain is entirely devoid of data save for a citation to a paper by Schenk et al.,[1]

[1] Schenk is the inventor of the present claims. Applicant reserves the right to show that Schenk et al. reference cited by Chain is not prior art to the present claims should this become relevant.

which described results from immunization with Aβ42 but not fragments thereof. Frenkel provides only *in vitro* aggregation experiments that do not resolve such questions as whether anti-aggregating activity of an antibody *in vitro* is correlated with useful therapeutic effects of the antibody *in vivo*. Collier and Van den Dobbelsteen may indicate that CRM197 is useful for generating an immune response for certain polypeptides but does not specifically address Aβ1-7, nor provide any indication whether an immune response to this peptide would be useful for treating Alzheimer's disease. For these reasons, applicant respectfully submits that the references did not provide a reasonable expectation of success of treating Alzheimer's disease using the claimed compositions.

Claims 120 and 132 stand rejected over the previous combination of references in further view of Potter and Restifo. Potter and Restifo are cited as teaching that the immunogenicity of small peptides can be increased by using multiple copies of the peptides. Without agreeing with this view, applicant submits that claims 120 and 132 would have been nonobvious for at least the same reasons as claims 119.

Claims 125 and 138 stand rejected over the Chain as evidenced by Alberts in view of Frenkel, collier and Van den Dobbelsteen in further view of Peters. Peters is alleged to teach the effect of four chemical crosslinkers on immunogenicity of peptide-carrier conjugates. Without agreeing with this view, applicant submits that claims 125 and 138 would have been nonobvious for at least the same reasons as claim 119.

Claim 133 is rejected as allegedly obvious over Chain as evidenced by Alberts in view of Frenkel, Collier and Van den Dobbelsteen in further view of Kensil. Kensil is alleged to teach QS-21 as an adjuvant. Without agreeing with this view, applicant submits that claim 133 would have been nonobvious for at least the same reasons as claim 119.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,

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